REMARKS

Claims 1-45 are pending in the present application. Claims 3, 13, 21 and 34 are amended, without prejudice or disclaimer of any previously claimed subject matter. Claims 4-6, 14-16, 22-24 and 35-37 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as directed to a non-elected invention. After entry of the amendment, Claims 1-3, 7-13, 17-21, 25-34 and 38-45 remain pending.

Claims 1-3 and 7 are directed to a method of selectively inducing apoptosis of a malignant cell comprising administering to a malignant cell a calcium-activated potassium channel activator in an amount sufficient to induce apoptosis of the cell.

Claims 8-13 are directed to a method of selectively inhibiting the proliferation of malignant cells compared to non-malignant cells in a mixed population of malignant and non-malignant cells, comprising administering to the mixed population of malignant and non-malignant cells a calcium-activated potassium channel activator in an amount sufficient to induce apoptosis of at least a plurality of malignant cells compared to non-malignant cells, thereby selectively inhibiting the proliferation of malignant cells.

Claims 17-21 and 25-32 are directed to a method of inhibiting the growth of a malignant tumor in a mammalian subject, comprising administering to a mammalian subject having a malignant tumor that comprises a malignant cell, a calcium-activated potassium channel activator under conditions and in an amount sufficient to induce apoptosis of the cell, whereby growth of the malignant tumor is inhibited.

Claims 33-34 and 38-45 are directed to a method of inhibiting the growth of a glial tumor in a mammalian subject comprising administering to a mammalian subject having a glial tumor that comprises a malignant cell, a calcium-activated potassium channel activator under conditions and in an amount sufficient to induce apoptosis of the cell, whereby growth of the malignant tumor is inhibited.

Rejection under 35 USC § 112

Claims 3, 13, 21 and 34 have been rejected 35 USC § 112, second paragraph, as indefinite. The Examiner suggests that the use of a laboratory designation (i.e., NS-1619) to identify a particular compound renders the claim indefinite because different laboratories may use the same laboratory designation to define completely distinct molecules. In view of the Examiner's objections, Applicants have amended Claims 3, 13, 21 and 34 to recite the chemical name of NS-1619, i.e., 1,3-dihydro-1-[2-hydroxy-5-(triflouromethyl)phenyl]-5-(triflouromethyl)-2H-benzimidazol-2-one.

The Examiner has further rejected Claims 1, 3, 7-13, 17-21 and 25-32 under 35 U.S.C. § 112, first paragraph, as non-enabled. The Examiner suggests that while the pending claims are enabled for a method of inducing apoptosis or inhibiting the proliferation of a glioma cell or tumor by administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619, it would be unpredictable whether the invention would be applicable to inhibiting the proliferation or inducing apoptosis of any malignant cell or tumor by administering a calcium-activated potassium channel activator (emphasis supplied).

In response to the enablement rejection, the Applicants submit that the method of the present invention is applicable to a wide variety of malignant cells and tumors. Until the Applicants' discovery thereof, it was not known that K_{CA} channel expression is more abundant in neovasculature and malignant cells compared to normal tissue. As shown in the '961 application, immunohistochemical results establishing over-expression of K_{CA} channels in glioma-bearing rat brain sections are consistent with results showing that activation of K_{CA} channels by a K_{CA} activator (NS-1619) selectively induced apoptosis in malignant cells compared to normal cells. Nor is this observation limited to glioma cells or glial tumors. As established in the Declaration of Keith L. Black, M.D. that accompanies this response, K_{CA} channels are also over-expressed on metastatic brain tumors of diverse origin, including both breast and lung metastatic brain tumors. No detectable K_{CA} channel expression is found in the brain tissue peripheral to the tumor periphery. In view of this evidence, Applicants believe that the claims are enabled for inducing apoptosis or inhibiting proliferation or growth of malignant cells or tumors generally.

In support of the enablement rejection, the Examiner notes that there are a number of other potassium channels involved in apoptosis of malignant cells or tumors, citing various references disclosed in the '961 specification. Applicants submit that none of the cited references teach a role for K_{CA} channels in apoptosis. Rather, these references relate to other types of potassium channels (e.g., $K_v1.3$ voltage gated channels) distinct from calcium-activated potassium (K_{CA}) channels. Moreover, some of these references suggest that activators of these other types of potassium channels (e.g., K_{ATP} potassium channels) actually prevent apoptosis, rather than inducing it. Others suggest that inhibitors of these other types of potassium channels (e.g., Kv1.5 delayed rectifier potassium channels) induce apoptosis. Clearly, the contrary and varied effects observed in these studies indicate that the role of even these non- K_{CA} potassium channels was unclear at the time the application was filed. More importantly, no role for K_{CA} channels in apoptosis, or their modulation by K_{CA} activators to induce apoptosis, is suggested.

Conclusion

In light of the comments provided herein, Applicants request that the Examiner now allow all pending claims.

Respectfully submitted,

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